



Case Fatality Rate and Length of Hospital Stay among Patients with Typhoid Intestinal Perforation in Developing Countries: A Systematic Literature Review

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Abstract

Background: Typhoid fever remains a major health problem in the developing world. Intestinal perforation is a lethal complication and continues to occur in impoverished areas despite advances in preventive and therapeutic strategies.

Objectives: To estimate the case fatality rate (CFR) and length of hospital stay among patients with typhoid intestinal perforation in developing countries.

Data Sources: Peer-reviewed publications listed in PubMed and Google Scholar.

Study Eligibility: The publications containing data on CFR or length of hospitalization for typhoid fever from low, lower middle and upper middle income countries based on World Bank classification. Limits are English language, human research and publication date from 1st January 1991 to 31st December 2011.

Participants: Subjects with reported typhoid intestinal perforation.

Interventions: None, standard practice as reported in the publication.

Study Appraisal and Synthesis Methods: Systematic literature review followed by meta-analysis after regional classification on primary data. Descriptive methods were applied on secondary data.

Results: From 42 published reports, a total of 4,626 hospitalized typhoid intestinal perforation cases and 706 deaths were recorded (CFR = 15.4%; 95% CI; 13.0%–17.8%) with a significant regional differences. The overall mean length of hospitalization for intestinal perforation from 23 studies was 18.4 days (N = 2,542; 95% CI; 15.6–21.1).

Limitations: Most typhoid intestinal perforation studies featured in this review were from a limited number of countries.

Conclusions: The CFR estimated in this review is a substantial reduction from the 39.6% reported from a literature review for years 1960 to 1990. Aggressive resuscitation, appropriate antimicrobial coverage, and prompt surgical intervention may have contributed to decrease mortality.

Implications: The quantification of intestinal perforation outcomes and its regional disparities as presented here is valuable in prioritizing and targeting typhoid-preventive interventions to the most affected areas.

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Introduction

Typhoid fever is caused by the gram negative bacillus *Salmonella enterica* serovar Typhi (*S. typhi*) [1] continues to be a public health problem in developing countries [2]. It is transmitted via the faeco-

oral route through ingestion of contaminated food or water. The disease is characterized by prolonged fever, and constitutional symptoms including headache, anorexia and abdominal pain [3]. The systemic involvement in typhoid fever can result in extra-intestinal complications such as encephalopathy, meningitis,

hepatitis, myocarditis and pneumonia, while the most common gastro-intestinal complication is haemorrhage [4]. Intestinal perforation is a potentially fatal complication of typhoid fever secondary to the inflammation and necrosis of Peyer's patches when not treated early and appropriately. Generally, perforation is a late complication occurring in the third week of illness, though it is reported earlier in second week in developing countries for reasons that are not completely understood [4,5,6,7].

Case fatality rate (CFR) in intestinal perforation is dependent on various factors such as the quality of health care service received, characteristics of the organism and host factors. The diagnostic and therapeutic management for intestinal perforation have changed significantly over the past three decades which has potential implications on morbidity, mortality, hospital costs and societal costs. Aggressive resuscitation and prompt surgical intervention within the first 24 hours of perforation, along with appropriate antimicrobial coverage, are considered key measures in intestinal perforation management in recent days [8,9,10,11]. The appearance and spread of multidrug resistant *S. typhi* strains is another factor that influences outcomes of typhoid intestinal perforation. Multidrug resistant strains exhibiting resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole have emerged in South East Asia since the late 1980s. They have subsequently spread to other regions of the world, affecting morbidity, mortality and duration of treatment [12,13,14]. Poorer outcomes have been observed in those with late presentation (≥ 24 hours since perforation) [9,15], multiple perforations (>1) [11,15,16,17], and post-operative complications such as faecal fistula [15,18].

A worldwide case series from 1960–90 had reported 1,990 cases of intestinal perforation in 66,157 patients with typhoid fever [19]. The publication reported a 3% perforation rate and a 39.6% CFR among typhoid perforation cases, noting an overall male preponderance. Advanced perforation management and emerging multidrug-resistant *S. typhi* in recent years could potentially modify characteristics of typhoid intestinal perforation and CFR. We present an updated review of CFR, age and gender characteristics, and length of hospital stay associated with typhoid intestinal perforation by geographical regions from articles published from 1991 to 2011 in low income, lower middle income and upper middle income countries [20].

Methodology

Search strategy and selection criteria

A systematic literature review was carried out using PubMed electronic database for typhoid fever intestinal perforation related publications in English from 1st January 1991 to 31st December 2011. The search was repeated using the Google Scholar electronic database for additional publications. The key terms used in the search were “Typhoid Fever”, “Enteric Fever”, “Salmonella Typhi”, and “Intestinal Perforation”. The selection criteria and search terms for the study inclusion are listed in Table 1. Two researchers conducted independent reviews based on defined search strategy and criteria, and compared the results before selecting final papers. One researcher extracted data and another researcher matched the data with original papers to verify for its correctness. No written protocol was developed.

Analytical method

An important aspect of this review was to capture the regional differences in CFR due to typhoid intestinal perforation, age and gender characteristics, and length of hospital stay. To identify the regional differences, we categorized the studies by geographical

regions, namely: Asian countries, African countries and countries in other regions.

We have deployed meta-analysis approach [21] for validating and summarizing results so that a regional comparison of variables can be made. In this review, we have applied heterogeneity test to compare dissimilarity between results extracted from various primary studies based on a random effect model. The heterogeneity test was utilised to verify the validity of results and to potentially eliminate the effect of study quality and publication bias (the association of publication probability with the statistical significance of study results) [22,23]. We considered the results of various studies comparable if no heterogeneity in the results was observed.

To perform meta-analysis, first, data on CFR, male to female ratio, age and length of stay in hospitalized intestinal perforation cases were extracted from selected publications. The data was classified by three geographical regions and listed in descending chronological order of year of publication. Then, the test for heterogeneity was conducted for CFR and male to female ratio to explore the true effects. The mean and corresponding 95% confidence interval for individual studies were estimated based on a random effect model and a graphical overview of the results was obtained by forest plot. We did not estimate 95% confidence interval of individual studies and heterogeneity test by using meta-analysis for age and length of hospital stay as variance was not available.

The validated results from meta-analysis for various regions were compared using Kruskal-Wallis test [24] to assess whether there was a significant difference in results from different geographical regions. If a significant difference between regions was observed, a simultaneous multiple paired comparison was performed to test inequalities between three possible combinations of two regions each. We applied nonparametric Kruskal-Wallis test on CFR, male to female ratio, age and length of hospital stay to compare the three regions. The box plot was generated to show data dispersion within each region and the strength of linear relationship between time and perforation outcome was tested using Spearman correlation coefficient [25,26].

The analysis was performed using statistical software R while all statistical comparisons were tested for overall significance level at 5% ($\alpha = 0.05$).

The selected papers had some additional information on the characteristics of intestinal perforation such as presenting symptoms, duration of illness, management procedures and post-operative complications. These features were summarized using descriptive methods.

Results

A total of 3,941 results on typhoid fever were narrowed down to 168 publications pertaining to typhoid intestinal perforation. When 168 abstracts were reviewed, we found 37 eligible papers based on the selection criteria. Supplementary literature search using Google Scholar identified 220 papers from which 9 additional papers were found eligible for the review (Figure 1).

Upon review of the 46 papers identified from low income, lower middle income and upper middle income countries, we found two of the papers analysed the same data set [27,28]. We chose the article with the most comprehensive information [28]; noted in the figure 1 as exclusion based on common dataset. An additional two papers were excluded as they had presented CFR in specific surgical procedures that could not be generalized [29,30]; noted in the figure 1 as exclusion based on being not generalizable. One study presenting 12 typhoid perforation cases in a tertiary hospital

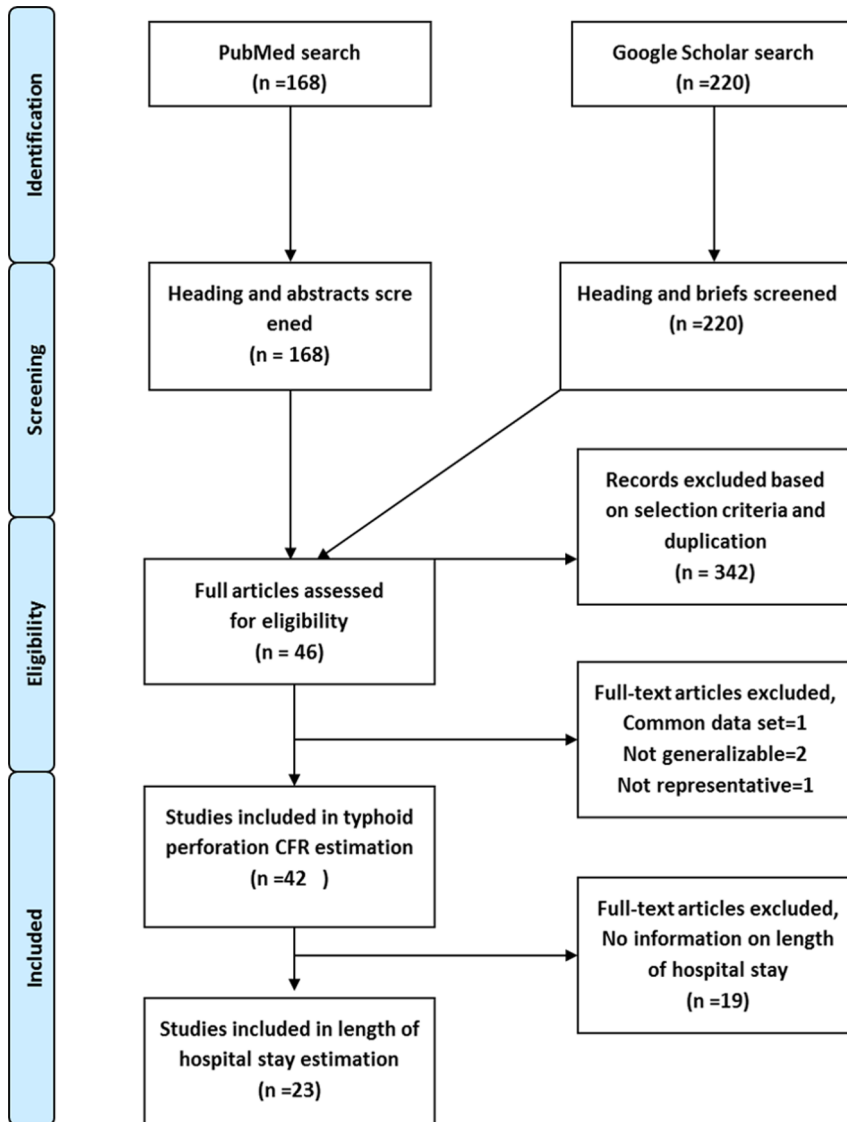
Table 1. Selection criteria for study inclusion.

Selection criteria
• Published in English in peer reviewed journal from 1 st January 1991 to 31 st December 2011
• Presents typhoid intestinal perforation case fatality rate or length of stay in hospitalized patients
• Includes data at least from 1990 or afterwards
• Contains data from low income, lower middle income and upper middle income countries based on World Bank classification- "Country and Lending Groups by income", 2011 [20].
Search terms in PubMed
• ((Typhoid fever) OR (Enteric Fever) OR (Salmonella Typhi)) AND ((Intestinal perforation) OR (perforation))

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in Nigeria with an outlier CFR was excluded since the study population was not representative. These subjects were referred late, presenting in critically ill condition after treatment failure [31]. Of the remaining 42 papers included in final review (Table 2)

[5,6,7,11,15,16,17,18,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63], twelve articles contained data from before and after 1990 [6,7,15,35,45,46,48,49,58,60,62,63]. Though the analysis pre-

**Figure 1.** Study selection flow diagram. CFR = case fatality rate.

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Table 2. Case fatality rate (CFR) in hospitalized typhoid intestinal perforation cases by study (1991–2011).

Country	Year of publication	Study period	Hospitalized typhoid perforation cases	Deaths	CFR	Reference
Africa						
Nigeria	2011	2002–2009	153	16	10.5%	[18]
Nigeria	2010	2004–2008	46	13	28.3%	[32]
Ghana	2009	2000–2005	650	82	12.6%	[33]
Nigeria	2008	1990–2004	105	14	13.3%	[34]
Nigeria	2008	1995–2004	89	17	19.1%	[17]
Nigeria	2007	1996–2005	184	42	22.8%	[5]
Nigeria	2007	1980–2005	20	4	20.0%	[35]
Ghana	2007	2001–2005	522	61	11.7%	[36]
Nigeria	2007	2004–2006	53	8	15.1%	[11]
Ghana	2007	2002–2005	248	27	10.9%	[37]
Togo	2005	2003	112	18	16.1%	[38]
Nigeria	2005	1994–2003	101	14	13.9%	[39]
Nigeria	2004	1997–2003	47	6	12.8%	[40]
Ivory Coast	2004	1995–1998	64	22	34.4%	[41]
Nigeria	2004	1996–2000	43	6	14.0%	[42]
Nigeria	2003	1998–2001	105	17	16.2%	[43]
Nigeria	2003	1990–2000	108	27	25.0%	[44]
Nigeria	2002	1989–1998	60	15	25.0%	[45]
Nigeria	2001	1984–1999	106	25	23.6%	[6]
Ethiopia	2000	1984–1995	27	10	37.0%	[46]
Nigeria	1999	1987–1996	64	25	39.1%	[7]
Nigeria	1998	1991–1994	75	15	20.0%	[47]
Nigeria	1997	1989–1990	50	14	28.0%	[15]
Nigeria	1992	1986–1990	18	5	27.8%	[48]
Ghana	1992	1978–1991	195	61	31.3%	[49]
Asia						
Pakistan	2009	2003–2008	44	6	13.6%	[50]
Pakistan	2006	2003–2005	112	8	7.1%	[51]
Nepal	2006	2002–2004	102	7	6.9%	[16]
Pakistan	2006	1998–2000	32	4	12.5%	[52]
Pakistan	2005	2002–2004	72	10	13.9%	[53]
Vietnam	2004	1997–1998	27	1	3.7%	[54]
India	2003	2000–2001	200	21	10.5%	[55]
India	2001	1990–1998	100	7	7.0%	[9]
Pakistan	2000	1991–1994	76	17	22.4%	[56]
India	1997	1990–1995	110	18	16.4%	[28]
Pakistan	1997	1994–1995	140	12	8.6%	[57]
India	1994	1987–1990	65	13	20.0%	[58]
Others						
Turkey	2010	1994–2010	22	1	4.6%	[59]
Turkey	2007	1978–2004	82	9	11.0%	[60]
Turkey	2002	1990–2000	42	2	4.8%	[61]
Mexico	1998	1985–1994	116	2	1.7%	[62]
Turkey	1995	1987–1993	39	4	10.3%	[63]
Overall			4,626	706		

Note: Studies are listed in the table by descending order of publication year.
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Table 3. Length of hospital stay among typhoid intestinal perforation cases by study (1991–2011).

Country	Age range (mean)	Number of cases	Mean length of stay (days)	Range of length of stay	Study period	Year of publication	Reference
Africa							
Nigeria	3–15 (9.6)	153	21.0	8–67	2002–2009	2011	[18]
Nigeria	9–15 (9.5)	46	22.9	4–46	2004–2008	2010	[32]
Ghana	1–15 (8.8)	650	14.4	1–77	2001–2005	2009	[33]
Nigeria	15–72 (27)	105	16.1	NA	1990–2004	2008	[34]
Nigeria	1–15 (9.1)	89	22.0	18–42	1995–2004	2008	[17]
Nigeria	4–15 (6.8)	184	35.8	8–196	1996–2005	2007	[5]
Nigeria	2–55 (12.3)	53	16.1	8–57	2004–2006	2007	[11]
Nigeria	11–45 (25.7)	20	16.3	0–32	1980–2005	2007	[35]
Ghana	16–55 (24.9)	248	12.4	5–46	2002–2005	2007	[37]
Nigeria	4–85 (19.9)	101	18.0	NA	1994–2003	2005	[39]
Ivory Coast	5–63 (34)	64	30.0	8–52	1995–1998	2004	[41]
Nigeria	6–32 (15.9)	43	21.6	8–74	1996–2000	2004	[42]
Nigeria	3–14 (8.8)	105	24.6	11–54	1990–2000	2003	[44]
Nigeria	1–67 (24.3)	60	11.7	1–60	1989–1998	2002	[45]
Nigeria	3–14 (10)	106	23.6	NA	1984–1999	2001	[6]
Nigeria	1–12 (8)	64	20.6	12–48	1989–1998	1999	[7]
Asia							
Pakistan	10–45 (29.4)	44	17.6	NA	2003–2008	2009	[50]
Nepal	14–78 (28.4)	102	8.5	NA	2002–2004	2006	[16]
Pakistan	15–30	32	16.5	NA	1998–2000	2006	[52]
India	5–58 (24.0)	110	15.8	NA	1990–1995	1997	[28]
Others							
Turkey	7–68 (36.3)	82	11.7	5–25	1978–2004	2007	[60]
Turkey	4–14 (10.4)	42	13.4	7–23	1990–2000	2002	[61]
Turkey	3–76	39	12.0	NA	1987–1993	1995	[63]

SD = standard deviation, NA = not available. Note: Studies are listed in the table by descending order of publication year.
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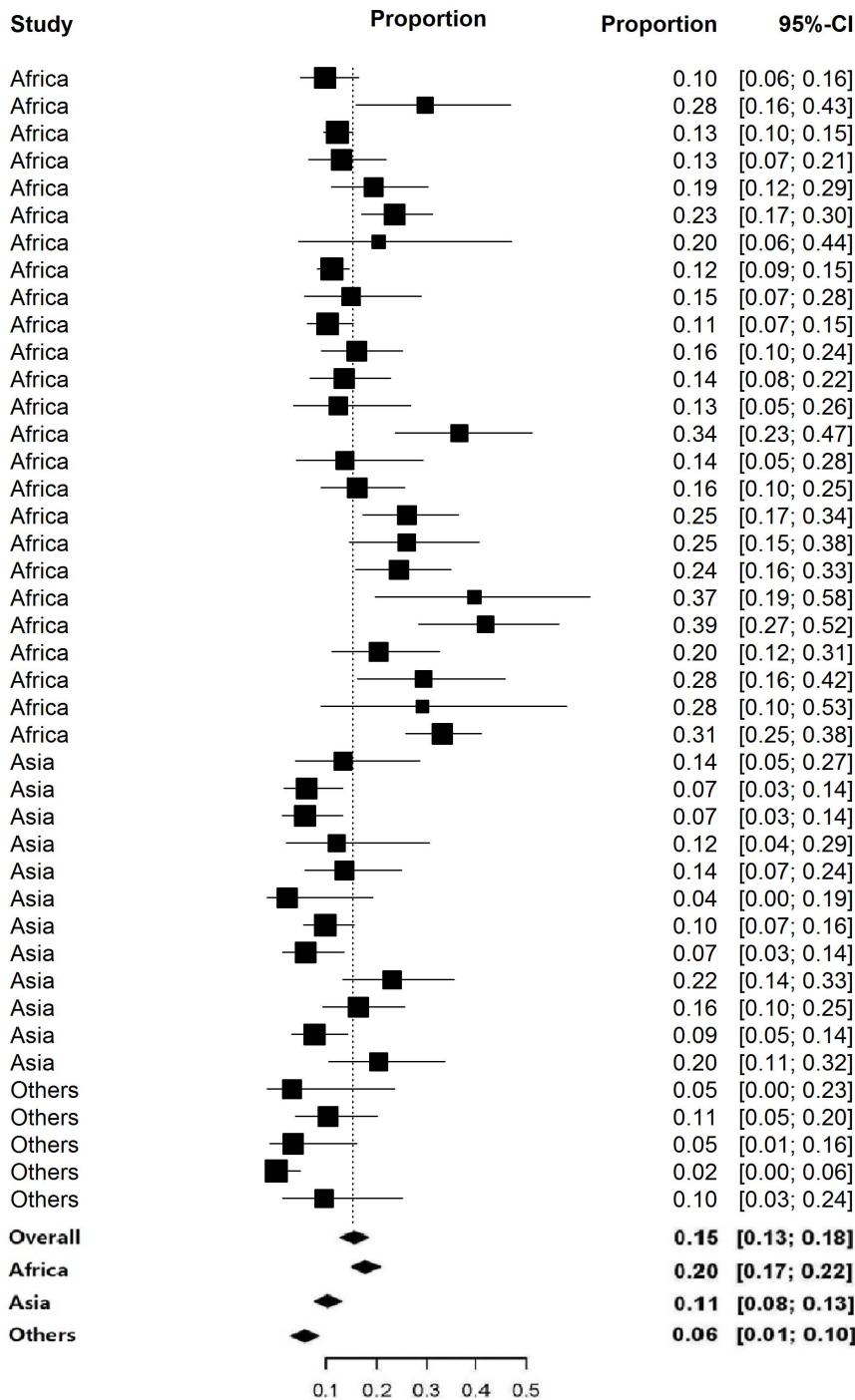


Figure 2. Forest plot showing mean case fatality rate for intestinal perforation along with 95% confidence interval based on studies published from 1991 to 2011.
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dominantly included data after 1990, the complete period ranged from 1978–2010. Of these 42 papers, 23 presented data on length of hospital stay (Table 3) [5,6,7,11,16,17,18,28,32,33,34,35,37,39,41,42,44,45,50,52,60,61,63].

The majority of publications came from five countries: Nigeria, Ghana, Pakistan, India and Turkey. We categorized 4,626 typhoid intestinal perforation cases from 11 countries into three geographical regions, Africa, Asia and others (Table 2). Two studies that assessed socio-economic status reported that around 78% to 88%

of typhoid intestinal perforation cases were observed among people from low socio-economic strata [39,45].

The common presenting symptoms of typhoid intestinal perforation in the reviewed papers were fever, abdominal pain, diarrhoea, constipation, vomiting and abdominal distension. The mean duration from the onset of illness to the presentation of typhoid perforation at hospital was 10.6 days (SD = 2.1, min = 7.4, max = 15.7) from 1,925 cases reported in 25 studies. Over the years, aggressive surgical procedures became popular over

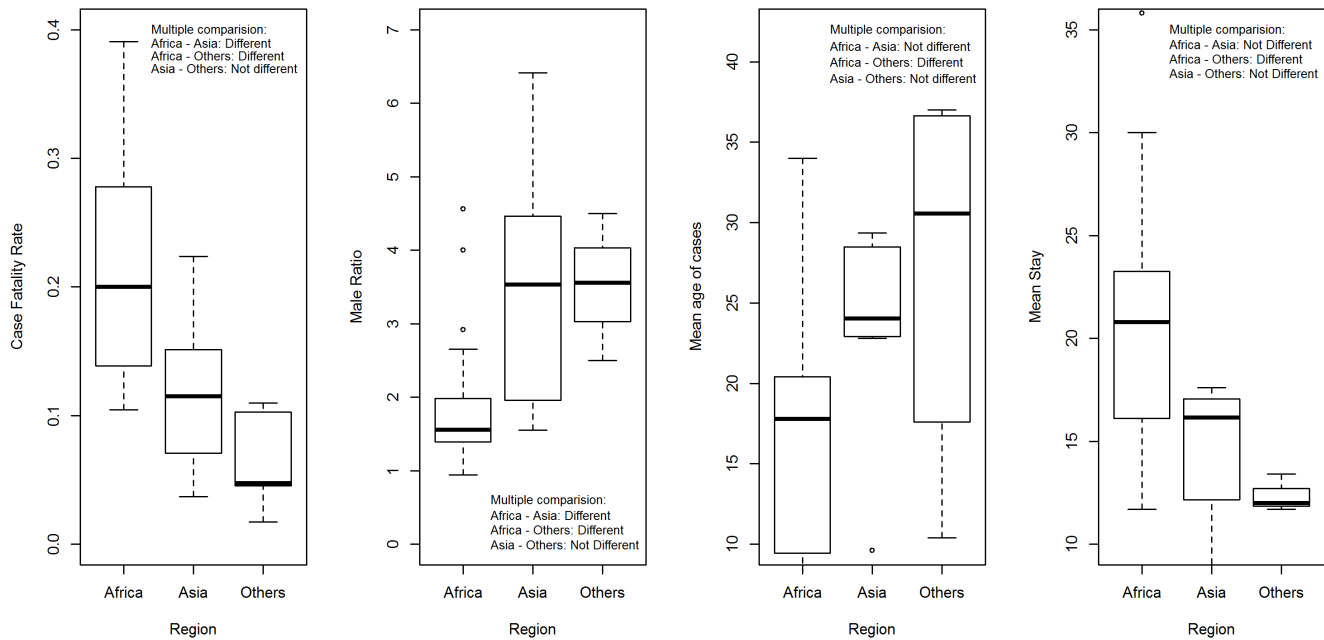


Figure 3. Box plot showing multiple comparisons between regions for case fatality rate, male to female ratio, mean age and mean length of hospital stay based on studies published from 1991 to 2011.
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conservative methods and simple drainage [8,9,27,48,63]. Among 26 papers that described surgical procedures, 23 reported simple closure or two layered closure as the most practiced surgical procedure. Solitary perforations were observed in 76% of the operated typhoid perforation cases that reported number of perforations per case ($N=2,903$), while the remaining cases involved multiple perforations. Postoperative complications were common and were reported in at least 57% of the 2,063 cases that described the complications. The common complications were: wound infection, wound dehiscence (breaking open of the wound along surgical suture), persistent peritonitis, intra-abdominal abscess and entero-cutaneous fistula, all of which were often associated with increased hospital stay [6]. Around 18% (140/792) of operated perforation cases were re-operated due to the complications [17,18,32,34,37,47,56] while, re-perforation was observed during the surgery in half (52/98) of the reported re-operated cases [37,56].

The overall mean CFR among typhoid perforation cases was 15.4% (95% CI; 13.0%–17.8%), with the highest rates observed in African countries (19.5%; 95% CI; 16.6%–22.4%) followed by Asian countries (10.7%; 95% CI; 8.0%–13.4%) and countries from other regions (5.55%; 95% CI; 1.45%–9.65%), (Table 4). The meta-analysis showed a significant heterogeneity in between the published studies in both Africa and Asia (Table 4) and the forest plot (Figure 2) indicated that point estimates do not have high credence. Overall mean CFR between three regions was significantly different as shown by nonparametric Kruskal-Wallis test (Table 4). The box plot showed that the CFR of Africa derived the significant difference from that of other two regions (Figure 3).

To estimate trends in CFR, a scatter plot of CFR in patients with perforation against time was drawn for African and Asian regions applying the rate to the final year of the study period. The Spearman correlation coefficient of CFR were -0.68 ($p < 0.01$) and -0.4 ($p = 0.2$) for Africa and Asia respectively which indicates a declining trend in CFR of typhoid intestinal perforation

(Figure 4). The decline is statistically significant in African region only.

Papers presenting information on gender ($n=40$), suggested that males were 2.16 times more likely to be hospitalized compared to females (95% CI=1.1–4.0) for typhoid intestinal perforation (Table 4). The male to female ratio was significantly higher in Asia and other regions compared to Africa, while there was no statistical difference between male to female ratio of hospitalized typhoid intestinal perforation cases between Asia and other regions (Figure 3).

Based on 35 studies reporting age data, the unweighted mean age of hospitalization among all patients was 19.3 years. The overall difference in reported age at hospitalization for intestinal perforation is significantly different between the regions ($p = 0.023$, Table 4). African region displayed a significantly lower mean age at hospitalization (Figure 3) compared to other regions.

Based on the review of 23 relevant papers, the longest duration of hospitalization following intestinal perforation was estimated in African region (20.4 days). The overall unweighted mean length of hospitalization from all studies was 18.4 days (Table 4). The mean of length of hospital stay was significantly higher in Africa compared to average length of hospital stay in other regions (Figure 3).

Several investigators in the African region have followed up intestinal perforation cases for a longer duration. They have reported deaths due to malnutrition, resulting either from an entero-cutaneous fistula or peristomal ulcerations [6,34,41]. Development of entero-cutaneous fistula was strongly linked with increased mortality [15,18,28,34]. While most studies describe deaths occurring within a few weeks following intestinal perforation, a cohort of 64 postoperative cases found considerable mortality of 3–6 months (64%) and after 6 months (27%) secondary to postoperative complications [41].

Table 4. Mean values for weighted case fatality rate, male to female ratio, age and length of hospital stay by region in studies published from 1991 to 2011.

Variables	Region	No. of Studies	Total (N)	Average (N)	Mean [95% CI]	Heterogeneity (p-value)	p-value [§]
Case fatality rate*	Overall	42	4626	110.1	0.154 [0.130; 0.178]	<0.001	<0.001
	Africa	25	3245	129.8	0.195 [0.165; 0.224]	<0.001	
Male to female ratio*	Overall	40	4456	111.4	2.160 [1.151; 4.031]	1.0	0.001
	Africa	25	3230	129.2	1.716 [0.777; 3.786]	1.0	
Weighted age (year)	Overall	35	4016	114.7	19.286 [16.329; 22.244]	0.979	0.023
	Africa	24	3218	134.1	16.697 [13.605; 19.787]		
Mean stay (day)	Overall	23	2542	110.5	18.374 [15.624; 21.124]	NA	0.030
	Africa	16	2091	130.9	20.443 [17.065; 23.821]		
Others	Overall	4	288	72.0	14.600 [8.022; 21.177]	NA	
	Africa	3	163	54.3	12.367 [10.113; 14.621]		

N = sample size, NA = not applicable,

* weighted mean,

§ region comparison by Kruskal-Wallis test.

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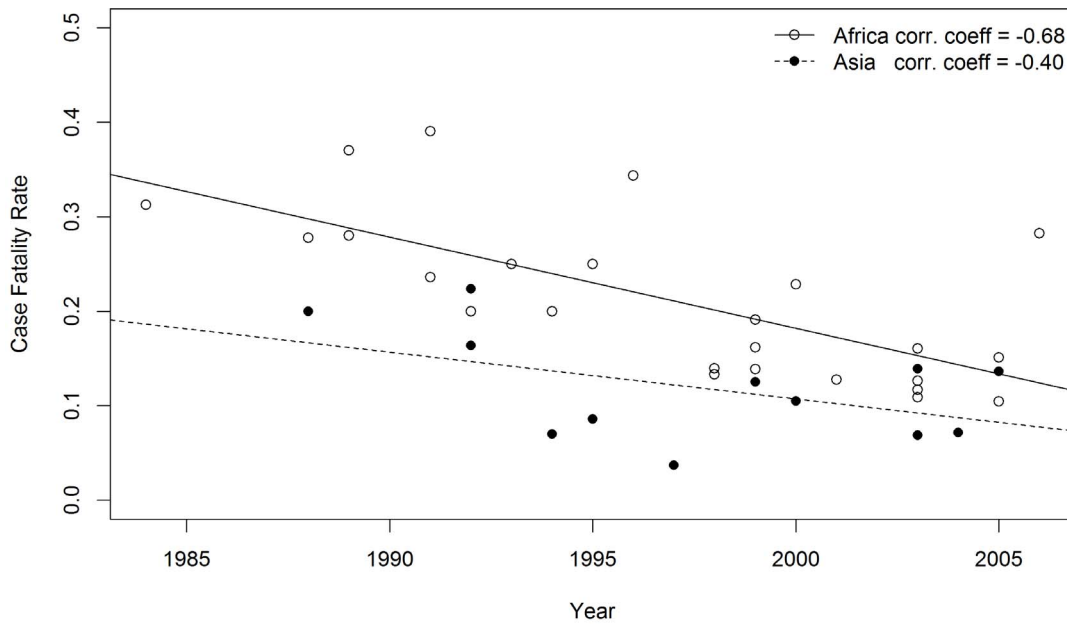


Figure 4. Trends of typhoid intestinal perforation case fatality rate in Africa and Asia from studies published from 1991 to 2011. Spearman Correlation coefficient was used to estimate strength of association. doi:10.1371/journal.pone.0093784.g004

Discussion

The review suggests a substantial reduction in typhoid intestinal perforation CFR from 39.6% reported from a literature review conducted for years 1960 to 1990 to 15.4% for years 1991 to 2011. The declining CFR trends in Africa and Asia within current review period indicates a gradual fall over the time. Based on a three-decade study, Chatterjee et al noted a declining trend of CFR in hospitalized typhoid perforation cases in India from 47.2% (1966–78) to 17.7% (1981–88) and 7% (1990–98) [9]. Our review denotes that the falling trend of typhoid intestinal perforation CFR is not confined to India, but also evident in other developing countries. As illustrated in the Indian case review mentioned above, improved typhoid perforation management practices over the years may be responsible for the positive effect in reducing the CFR and possibly offsetting increased complications due to multidrug resistance. Improving access to diagnosis, treatment and case management could further contribute to decrease in CFR.

While declining over the last five decades, this review indicates that even today more than one in 10 patients with typhoid intestinal perforation in Africa and Asia will die. The review also implies a high variability of perforation CFR within each of Africa, Asia and other regions; yet African region has significantly higher CFR. Not only people hospitalized for typhoid intestinal perforation seems younger in Africa compared to Asia and other regions, but also appear to stay longer in hospitals for treatment. The review suggests typhoid intestinal perforation occurs most commonly in the second week of illness, and is associated with a high proportion of postoperative complications.

This review has four important global public health implications. First, as noted above, typhoid intestinal perforation CFR is high even today in Africa and Asia, alerting to the importance of typhoid prevention and control activities in those regions. Second, it suggests that there is an opportunity to reduce typhoid intestinal perforation burden by improving access to care and management, such as aggressive resuscitation, better surgical facilities and use of

appropriate antibiotics. Third, it implies that a higher morbidity is likely to be shouldered in countries with increased length of hospital stays where younger people are affected. This is based on the fact that these longer hospital stays are associated with more severe disease or complications [6,11,34,37], which also imply higher treatment costs, and greater loss of productivity. Thus morbidity of typhoid could be significant enough to warrant prevention activities in some regions where even if incidence is not that high. Fourth, it provides some basic information needed for estimating disease and economic burden of typhoid in developing countries. The CFR is useful in model based estimation of typhoid intestinal perforation deaths at the country and regional levels. Length of hospital stay is useful in estimating direct medical costs and productivity loss associated with typhoid intestinal perforation. The significant difference in the characteristics of typhoid intestinal perforation between the regions, particularly between Africa and Asia, necessitates the need for separate regional data inputs in modelling the disease and economic burden.

This review also brings out an important research agenda. We noted delayed deaths even beyond six months occurring due to intestinal perforation, particularly as a result of malnutrition. However, most studies did not report follow-up results of patients for a long enough time to properly identify the delayed deaths. It is important to follow-up typhoid intestinal perforation cases for sufficient time to better understand the CFR in future studies.

Most intestinal perforation studies featured in this review are from one of three countries per continent. Nigeria, Pakistan and Turkey over represent Africa, Asia and the other regions, respectively. Thus, the regional average could be influenced by these selected countries in their respective sub-regions: West Africa, the Indian subcontinent and the Middle East. There were only a few studies from other regions which may bias the ability to draw meaningful conclusions due to limited data. The analysis includes only English literature and hence information published in other languages is not represented. This exclusion bias affects data from francophone Africa, from where only a handful of studies were published in English. Twenty three studies published

in languages other than English were excluded before screening, some of which might have contained data on typhoid intestinal perforation.

Because some studies containing data before and after the 1990 cut-off time point were included in the analysis, it should be noted that some data before the cut-off time (<1990) could have been included in the review. Though these reports did not separate the data by decade, the bulk of the data was within the review period (>1990). For this reason, we feel that the majority of cases reflect the time period of interest.

We may have slightly underestimated the length of hospital stay for intestinal perforation cases. Length of hospital stay could be shorter for those who died due to intestinal perforation than those who survived. Some of the studies presented here do not classify length of stay by survival state and therefore reports are inclusive of those who have died which are likely to be an underestimate.

Conclusion

This review estimated an overall average case fatality rate of 15.4% among hospitalized intestinal perforation cases with higher case fatality rates in African region followed by Asia. The results imply that younger people are hospitalized for typhoid intestinal perforation in Africa and remain hospitalized longer compared to Asia and other developing regions. Typhoid prevention activities

such as the provision of clean water, sanitation, personal hygiene measures, and vaccination should be prioritized in Africa as well as in Asia to limit number of deaths resulting from typhoid intestinal perforation. We emphasize the need for a regional approach in typhoid research, prevention and control activities. Estimation of regional typhoid disease and economic burden would be valuable in informing resource allocation strategies aimed at preventing and controlling typhoid.

Supporting Information

Checklist S1 PRISMA checklist.
(DOC)

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Author Contributions

Conceived and designed the experiments: VM TFW. Performed the experiments: VM VVM. Analyzed the data: JKP VM RLO. Contributed reagents/materials/analysis tools: VM SND VVM JKP RLO TFW. Wrote the paper: VM SND JKP VVM RLO TFW.

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